**REMARKS**

Initially, Applicants note that, once again, the Examiner has failed to acknowledge Applicants' claim to priority and receipt of the certified copy of the priority document.

As a result, the undersigned contacted the Examiner by telephone, and was advised that the priority document has indeed been received by the U.S. Patent and Trademark Office.

The Examiner indicated that she would shortly issue an Examiner's Interview Summary Record indicating the same.

Applicants have yet to receive the Interview Summary Record, and request that the same be provided with the next action.

In paragraph 2, on page 2 of the Office Action, the Examiner notes a minor typographical error in Claim 43.

Accordingly, Applicants hereby amend Claim 43 to correct this typographical error.

In paragraph 4, on page 2 of the Office Action, the Examiner rejects Claims 40-45 and 47-49 under 35 U.S.C. § 112, first paragraph.

Specifically, the Examiner states that the specification is only enabling for the use of Rp-8-Br-cAMPS, Rp-8-Cl-CAMPS and Rp-8-Br-monobutyryl-cAMPs in pharmaceutical compositions and in methods for treatment of CVI, AIDS or HIV infection for the inhibition of PKA type 1α. The Examiner contends that the specification does not provide enablement for the breath of the claimed pharmaceutical compositions and methods of treatment of any immunosuppressive disease or the inhibition of any effects mediated by PKA type 1α isozyme, as broadly claimed.

The Examiner further contends that the specification does not teach the use of the claimed compounds Rp-monobutyryl-cAMPS, Rp-8-(4-chlorophenyl-thio)-cAMPS and Rp-piperidino-cAMPS; or any other thio-substituted cAMP analog or an equatorial diastereomer of 3',5'-cyclic adenosine monophosphorothionate.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Applicants respectfully submit that the Examiner's rejection is legally improper, since it is not necessary to provide evidence with respect to each and every compound claimed. Rather, it is only necessary to provide data with respect to a representative number of compounds. Applicants respectfully submit that they have indeed provided data with respect to a representative number of compounds, and thus met their burden.

In any event, the Examiner is requested to note that independent composition Claim 40 and method Claim 43 are limited to five compounds, whereas independent method Claim 45 is broader with respect to the compounds, reciting only a cAMP antagonist. Furthermore, independent Claim 45 is limited to the three diseases, i.e., AIDS, HIV infection and CVI.

Applicants note that the Examiner cites Gjersten et al as teaching the unpredictability of the use of cAMP antagonists. Thus, it is the Examiner's position that additional evidence needs to be provided to support the scope of the claims.

While it is apparent from Gjertsen et al that not all compounds work equally well to inhibit PKA I and II, only Rp-8-Br-cAMPS and Rp-8-Cl-cAMPS and Rp-$N^6$-phenyl-cAMPS were

tested therein to any rigorous degree. The initial experiment that was performed was a screen for identifying potentially useful agents; the ability of the compounds to antagonize glucagon-induced lowering of DNA replication in hepatocytes was assayed (glucagon is a cAMP elevating agent). This assay is useful to identify potent and cell permeable antagonists, but is not suitable to identify weak antagonists, nor does it distinguish between antagonists of PKA types I and II.

In Figure 3 of Gjertsen et al, all of the compounds tested are said to be antagonists of PKA I. Figure 3A shows Rp-cAMPS, Rp-8-Cl-cAMPS, Rp-8-Br-cAMPS and Rp-$N^6$phenyl-cAMPS all antagonize PKA type I. In Figure 1, however, Rp-$N^6$-phenyl-cAMPS is shown not to function as an antagonist of forskolin-induced cAMP actions in fibroblasts. There is thus, contradiction within Gjertsen et al as different results appear to be achieved by different methods. Hence, there is no clear data in Gjertsen et al that would support the Examiner's assertion of the unpredictability of the antagonist properties of these compounds.

Gjertsen et al is concerned with finding the most potent antagonist, and refers in this regard to the "first line" cAMP antagonist. This is not to say, much less demonstrate, that other compounds which are less potent, are not antagonists. Indeed, Gjertsen et al shows that not only it is easy to identify antagonists, but that a high proportion of cAMP analogues are antagonists. It should be noted that in no claim of the present application is reference made to a cAMP analogue *per se*. The claims of the present application refer to specific

compounds or refer generically to cAMP antagonists (see Claim 45). Thus, those compounds in Gjertsen et al which are cAMP analogues, but are not cAMP antagonists, are clearly outside of the scope of the present claims. Hence, the relevant teaching of Gjertsen et al may be distilled to the fact that antagonists of cAMP have variable potency. This is not contested. The fact that antagonistic activity is present inherently confers the ability to antagonize, and thus reduce PKA Type Iα signaling. In view of Applicants' discovery of the pivotal role of PKA Type Iα signaling in immunosuppressive diseases, the use of such antagonists to affect that signaling *in vitro* or *in vivo* is thus fully expected to elicit the desired increase in T-cell function. This is readily testable for individual antagonists, and has been borne out by a representative number of antagonists in the Declaration evidence filed June 19, 2002.

Applicants have already shown the efficacy of Rp-8-Br, Rp-8-Cl, and Rp-8-Br-monobutyryl cAMP analogues (see the Declaration evidence of record). Other compounds specifically mentioned in the claims are Rp-8-(4-chlorophenylthio) and Rp-piperidino cAMP analogues. The antagonistic capabilities of these compounds has now also been tested (as well as the Rp-8-Br and Rp-8-Cl cAMP analogues for comparative purposes). The attached Second Declaration provides data, which shows that Rp-8-Cl-cAMPS, Rp-8-Br-cAMPS, Rp-8-PIP-cAMPS, Rp-8-CPT-cAMPS and Rp-cAMPS all act as antagonists of PKAIα. Rp-cAMPS has been tested instead of Rp-monobutyryl-cAMPS, as the former is the physiologically relevant form, in view of the cleavage to remove

the monobutyryl moiety within the cell. Further information is also included in the Second Declaration showing the specificity of these compounds ($EC_{50}$ values, see the figures of the Second Declaration). Comparable *in vivo* results to those already shown, e.g., for the Rp-8-Br-cAMPS may also be expected for these antagonists.

While the Examiner states that one necessarily would practice *de novo* "trial and error" experimentation to make and use cAMPS analogs other than Rp-8-Br-cAMPS, Rp-8-Cl-CAMPS and Rp-8-Br-monobutyryl-cAMPS, this is not the standard for lack of enablment. The standard is whether or not it would require "undue" experimentation. Trial and error experimentation may be routine, and therefore not undue. In the context of the present invention, such would be simply routine experimentation.

Indeed this type of assay is set out in Gjertsen et al, see Figure 3 and the associated text. It is a relatively straightforward assay to perform and certainly could not be seen as undue experimentation. The Examples in the present application provide further types of assay that could be performed (e.g., testing T cell proliferation).

Hence, Applicants respectfully submit that the Examiner's rejection is improper.

In summary, as to claims directed to specific compounds, direct evidence of the antagonistic effect of each claimed compound has been provided. Direct evidence of *in vitro* efficacy of 3 of the 6 named compounds has been shown and directly supports the fact that the PKA Type Iα signaling is affected by these compounds. Further, it has been shown that

the desired effects are achieved *in vivo* with a representative compound. There is absolutely no evidence to suggest that any of the other specifically recited compounds will not achieve the expected effects *in vivo*. The compounds belong to a small closely related family, all of which are Rp-cAMPS compounds. In view of their strong structural similarity, and extensive supporting data for all, or at least a representative set of the claimed compounds, which could be further examined by well described methods without undue experimentation, Applicants respectfully submit the requirements for enablement have been fully and comprehensively met.

It should be noted with regard to Claim 43, all that is required is that the effects of PKA Type Iα signaling are mediated. Since all of the compounds claimed in Claim 43 have specifically been tested and found to have antagonists activity for that enzyme, full enablment for this particular use has been shown.

With regard to more general Claim 45, as mentioned above, only cAMP antagonists are claimed, and Applicants have shown as noted above, that these antagonists fulfil their promise both *in vitro* and *in vivo*. The identification and testing of compounds within that family is readily achievable. Applicants have identified the crucial role of PKA Type Iα in the pathology of immunosuppressive disorders. They thus, offer for the first time, a means of treating such disorders which requires antagonism of the identified signaling pathway. As such, the claim scope is entirely commensurate with the invention which has been made. Several examples of suitable compounds for this

purpose have been shown to be effective. Further, related compounds can be readily and routinely identified by the skilled person. The present application thus, provides the information and methods necessary to identify and test for suitable compounds without undue experimentation.

As to Claim 47, this claim is more specifically limited to Rp-cAMPS, a group which has been thoroughly investigated. Similarly, new Claim 51 is directed to Rp-8 substituted cAMPS compounds.

Accordingly, Applicants respectfully submit that claims are enabled by the present specification, and thus request withdrawal of the Examiner's rejection.

In paragraph 5, on page 6 of the Office Action, the Examiner rejects Claims 40-42 under 35 U.S.C. § 102(b) as being anticipated by Gjersten et al.

The Examiner contends that Gjersten et al teaches "injection fluids" and "infusion fluids" which the Examiner considers would be a "pharmaceutical" composition. Further, the Examiner states that while Gjersten et al does not teach the limitation "pharmaceutically acceptable amount" of the cAMP antagonist, Gjersten et al uses an amount of 0.5 to 1.0 mM, which the Examiner contends is equivalent to the concentration employed in the present invention.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

Gjertsen et al discloses compositions containing Rp-8-Br-cAMPS, Rp-8-CPT-cAMPS and Rp-8-Cl-cAMPS only for use in *in vitro* experiments. Thus, the compositions of Gjertsen et al

are not "pharmaceutical" compositions, as claimed in the present application. That is, a pharmaceutical composition must be one which is at least suitable for use in a clinical setting. Gjertsen et al does not teach or suggest such a composition.

More specifically, on page 20600, Gjertsen et al teaches that the antagonist was obtained from BIOLOG Life Science Institute. Applicants have contacted this company and have confirmed that the compounds they supply are not suitable for pharmaceutical administration (see the Declaration of Hans-Gottfried Genieger of record).

In order to use compounds from BIOLOG for *in vivo* use, they have to be specially prepared for that use. These compounds were prepared for Applicants by acid precipitation to rid them of endotoxin. The products were then endotoxin tested, subjected to sterile filtration, pH testing and other processes. For use in humans, the compounds would have to be made to GMP. The compounds which are pharmaceutical compositions and suitable for *in vivo* use thus, differ from test directly obtainable from BIOLOG as used by Gjertsen et al. The compounds used by Gjertsen et al are simply not suitable for *in vivo* use, as evidenced by the additional steps required to make such compositions.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Gjersten et al, and thus request withdrawal of the Examiner's rejection.

In paragraph 6, on page 8 of the Office Action, the Examiner rejects Claims 40-44 under 35 U.S.C. § 102(e) as being anticipated by Cho-Chung et al.

Specifically, the Examiner states that Cho-Chung et al teaches phosphorothioate derivatives of 8-halo-cAMP, preferably 8-Cl-cAMP and 8-Br-cAMP, and that the compositions thereof may be contacted with cells to inhibit cell proliferation and that they may be made as a pharmaceutical composition.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

It is well-settled law that the general disclosure (i.e., "phosphorothioate derivative of 8-halo-cAMP, preferably 8-Cl-cAMP and 8-Br-cAMP" in Cho-Chung et al) does not deprive a specific claim (e.g., Rp-8-Br-cAMPS) of novelty, where there are multiple compounds that could fall within the general disclosure and where the genus is not inherently limited to a very small number of compounds.

The phosphorothioate derivatives of 8-halo-cAMP taught in Cho-Chung et al include all cAMPS compounds and an 8-substituted halogen, i.e., fluoride, chloride, bromium, iodine or astatin. Further, there is no teaching in Cho-Chung et al of the diastereomer (Rp or Sp), as claimed in the present application. The family members encompassed by the genus of Cho-Chung et al may thus, include Rp-8-Br-cAMPS, Rp-8-Cl-cAMPS, Rp-8-I-cAMPS, Rp-8-F-cAMPS, Rp-8-At-cAMPS, Sp-8-Br-cAMPS, Sp-8-Cl-cAMPS, Sp-8-I-cAMPS, Sp-8-F-cAMPS, Sp-8-At-cAMPS. Furthermore, the term "phosphorodithioates" also encompasses phosporodithioates, i.e., Sp-8-Br-cAMPS2, Sp-8-Cl-cAMPS2, Sp-8-I-cAMPS2, Sp-8-F-cAMPS2, Sp-8-At-cAMPS2 would also be in the group. In total, this group has 15 members and the genus is not inherently limited to only a small number of compounds. As such, the

specific compounds recited in Claims 40-44 are not disclosed in Cho-Chung et al.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested in Chuo-Chung et al, and thus request withdrawal of the Examiner's rejection.

In paragraph 7, on page 11 (*sic 10*) of the Office Action, the Examiner indicates that Claims 45 and 47-49 are free of prior art.

In view of the amendments to the claims and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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Registration No. 30,764

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WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: November 6, 2003

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kjetil TASKÉN et al.

Appln. No.: 09/428,458

Filed: April 29, 1998

For: USE OF IMMUNOMODULATING AGENTS

Conf. No.: 4681

Group Art Unit: 1635

Examiner: Schmidt, M.

SECOND DECLARATION UNDER RULE 132

Assistant Commissioner
of Patents
P.O. Box. 1450
Arlington, Virginia 2231-1450

I, Kjetil TASKÉN, a Norwegian citizen of Brekketunet 11, N-1349, Rykkinn, Norway;

declare as follows:

1. I am an inventor on the present application. A first Declaration was filed in connection with this application on 19 June 2002. This second Declaration supplements the evidence provided in the first Declaration. I have reviewed the Office Action dated 6 May 2003 which issued on the above application, wherein the Examiner raised objections under 35 U.S.C. 112, first paragraph, that the specification does not enable performance of the invention as claimed and that Gjertsen et al teach the unpredictability of the use of cAMP antagonists in view of their differing abilities to antagonize the actions of cAMP on protein kinase A (PKA). Experiments have been carried out under my direction to illustrate the common antagonistic effect of a variety of Rp-cAMP analogues on PKA Type Iα activity by two different assays which determine $EC_{50}$ values of various Rp-cAMP analogues.

2. The purpose of the following analyses was to illustrate the antagonistic effect of Rp-cAMPS analogues on Type I (RIα/Cα) holoenzyme complexes of the cAMP-dependent protein kinase. The

extent of the antagonistic effect was measured by determining the $EC_{50}$ values using suppression or activation assays based on the so-called Cook assay.

3. The RIα holoenzyme complex for use in the experiments was prepared by overnight dialysis of PKA RIα and PKA Cα in a molar ratio of 1.2 to 1.0. Three 1 l buffer changes (dialysis buffer: 20 mM MOPS pH7.0, 150 mM NaCl, 5 mM $MgCl_2$, 100 µM ATP, 5 mM β-mercapto-ethanol) were carried out to remove the cAMP from the regulatory subunit.

4. The holoenzyme complex and the assay conditions were tested prior to conducting the analysis of the analogues as follows: Holoenzyme was diluted (dilution buffer: 100 mM MOPS pH 7.0; 10 mM Mg $Cl_2$, 1 mM ATP, 1 mM DTT) to a 1 µM stock solution and tested for activity in the spectrophotometric Cook assay (assay mix: 100 mM MOPS pH 7.0, 10 mM Mg $Cl_2$, 1 mM phosphoenol pyruvate, 1 mM ATP, 200 µM NADH, 1 mM DTT, 15 U/ml lactate dehydrogenase, 70 U/ml pyruvate kinase). The reaction was started by mixing 1 µl 25 mM kemptide (PKA substrate, LRRASLG) (200 µM final concentration of active peptide) to 1 µl holoenzyme (10 nM final concentration) in 100 µl total volume of assay mix. $OD_{340}$ was monitored for 1 minute and relative activity of Cα was plotted as the slope of OD-decay/minute. Only a small residual activity of Cα (<8% of the activated complex) showed a nearly complete formation of inactive holoenzyme complex.

4. The activation constant of cAMP was determined by using increasing concentrations of cAMP in a 3 minute preincubation with 10 nM holoenzyme in the assay mix. The results are shown in Annex 1, Figure 1. $EC_{50}$ denotes the concentration at which half-maximal activation was achieved in this method and was 88 nM.

5. For the assays, all Rp-cAMPS analogues were dissolved in dilution buffer with 20% DMSO to a final concentration of 10 mM and the concentrations were determined spectrophotometrically using molar extinctions coefficients at $\lambda_{max}$. Further dilutions of the Rp-cAMPS analogues were prepared by repeated 1:10 fold dilutions in

dilution buffer. Preferably 1 µl but not more than 5 µl of the test Rp-cAMPS analogue was added to the assay mix. Therefore the DMSO concentration in the final assay mix was not higher than 1%. The effect of DMSO on the assay enzymes was tested and the results showed that DMSO concentrations of 1% or more had no effect on the assay enzymes (ADP columns) or Holo RIα (Cα, Holo RIα and cAMP activated Holo RIα columns).

6. *Activation assay:* Rp-cAMPS analogues were screened to determine whether they behaved as antagonists or agonists. All Rp-cAMPS analogues were screened in an activation assay using 10 nM Holo RIα and 10 µM of each Rp-cAMPS analogue. None of the compounds behaved as agonists or partial agonists and did not activate PKA (data not shown).

7. *Suppression assay:* The antagonistic properties of the Rp-cAMPS analogues were characterized in detail using a suppression assay. 10 nM RIα holoenzyme was partially (80%) activated by addition of agonist - 1 µM Sp-8-Br-cAMPS (in the assay mix for three minutes). The holoenzyme was then reconstituted by the addition of the test Rp-cAMPS analogue (increasing concentrations ranging from pM to mM concentrations) for an incubation time of five minutes, before starting the assay of enzyme activity using the substrate kemptide. $EC_{50}$ determinations were carried out for the Rp-cAMPS analogues by the Cook spectrophotometric assay (described above). At least 10 measurements in duplicates were performed per analogue. In this assay, antagonists act by blocking binding and activation of PKA by Sp-8-Br-cAMPS by competitive antagonism and result in a decrease in kinase activity.

8. Rp-8-CPT-cAMPS (i.e. chlorophenylthio), Rp-8-Br-cAMPS, Rp-8-Cl-cAMPS, Rp-8-piperidino-cAMPS and Rp-cAMPS itself without any modifications were tested. The $EC_{50}$ value which is the concentration at which the activation is reduced to half its maximum was assessed. As can be seen from Annex 2, Figures 2 to 6, all the tested compounds work as effective antagonists of the PKA type Iα as assessed by this assay.

9. These results therefore show that a variety of cAMP analogues

have antagonistic and not agonistic effects on the PKA Type Iα enzyme. The presence and extent of antagonism is readily testable and was found to be present in all of the Rp-cAMP analogues described above. In view of the antagonistic properties of these analogues, a negative effect on the activity of PKA Type Iα and hence the signalling pathways in which that enzyme is involved may be expected when using these analogues *in vitro* or *in vivo* in cells employing that signalling involving PKA Type Iα. It is therefore fully expected that the *in vitro* and *in vivo* effects observed using other PKA Type Iα antagonists (as shown for example in my first Declaration) will also be achieved using PKA Type Iα antagonists such as those described in this Declaration in view of their comparable antagonistic properties.

10. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Codes, and that such wilful false statements may jeopardize the validity of the application and any patent issuing thereon.

Kjetil Taskén 10/23/2003

Kjetil Taskén Date

PATENT APPLICATION


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Kjetil TASKÉN et al.
Appln. No.: 09/428,458
Filed: April 29, 1998
For: USE OF IMMUNOMODULATING AGENTS

Conf. No.: 4681
Group Art Unit: 1635
Examiner: Schmidt, M.

ANNEX 1

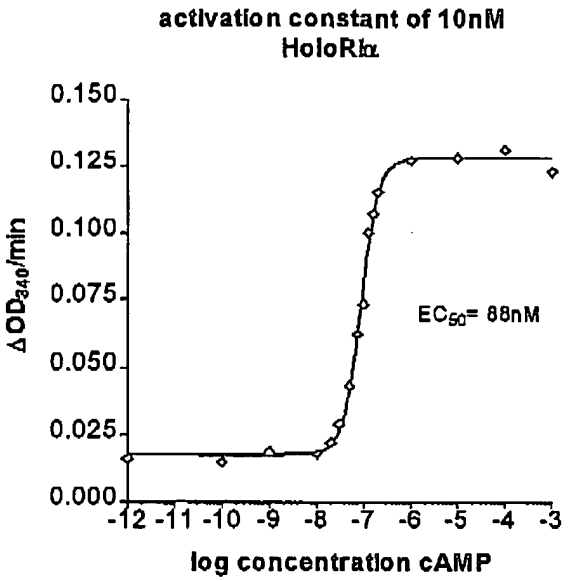


Figure 1: Determination of the activation constant of Holo RIα with cAMP. After a 3 minute preincubation of increasing concentrations of cAMP with 10 nM Holo RIα in assay mix the reaction was started by addition of 200 $\mu$M kemptide. $OD_{340}$ was monitored for 1 minute and the slope ($\Delta OD_{340}$/min) was plotted as a direct correlation of the relative activity of activated catalytic subunit.

PATENT APPLICATION

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ANNEX 2

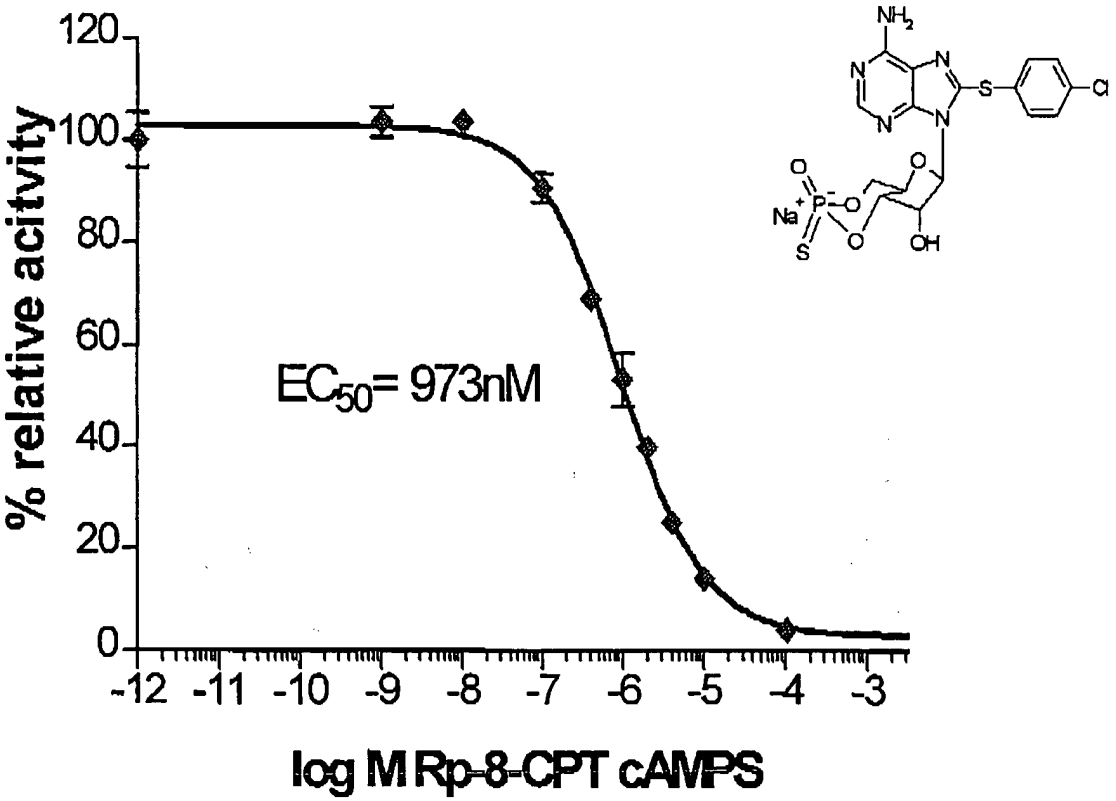


Figure 2

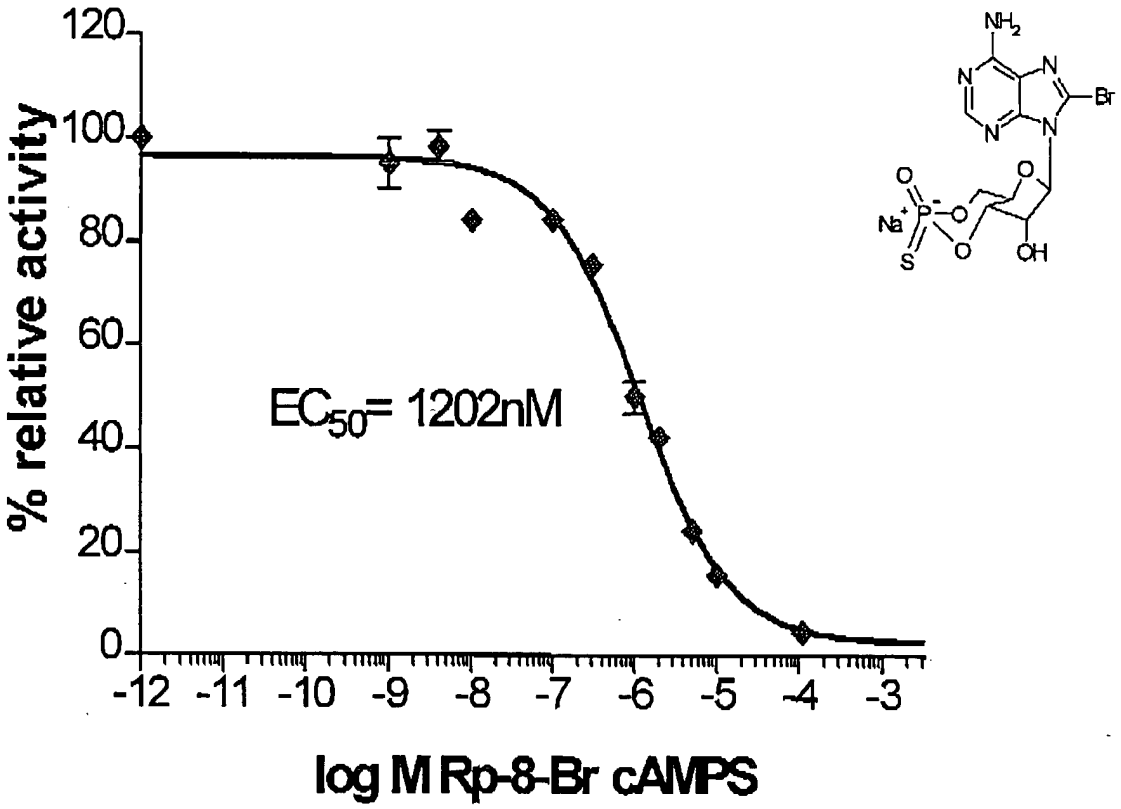


Figure 3

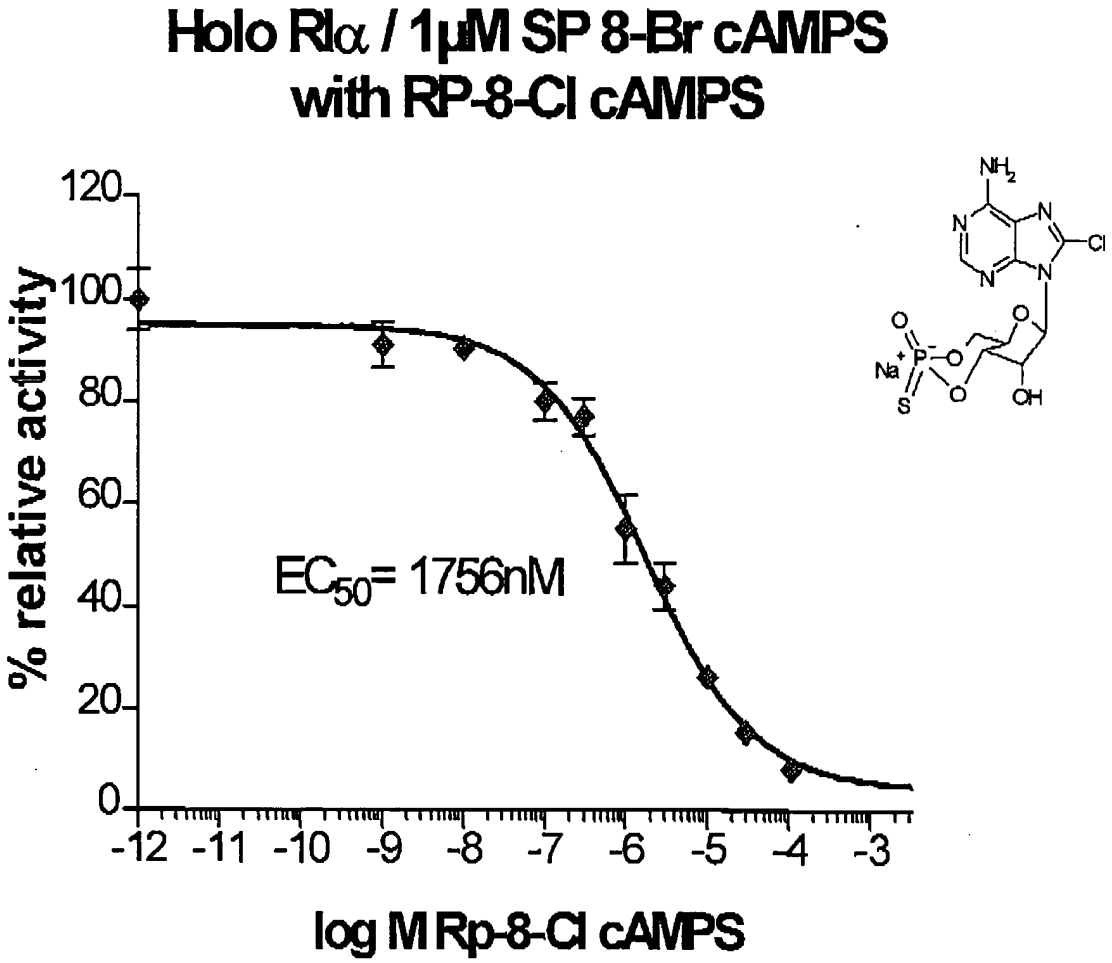


Figure 4

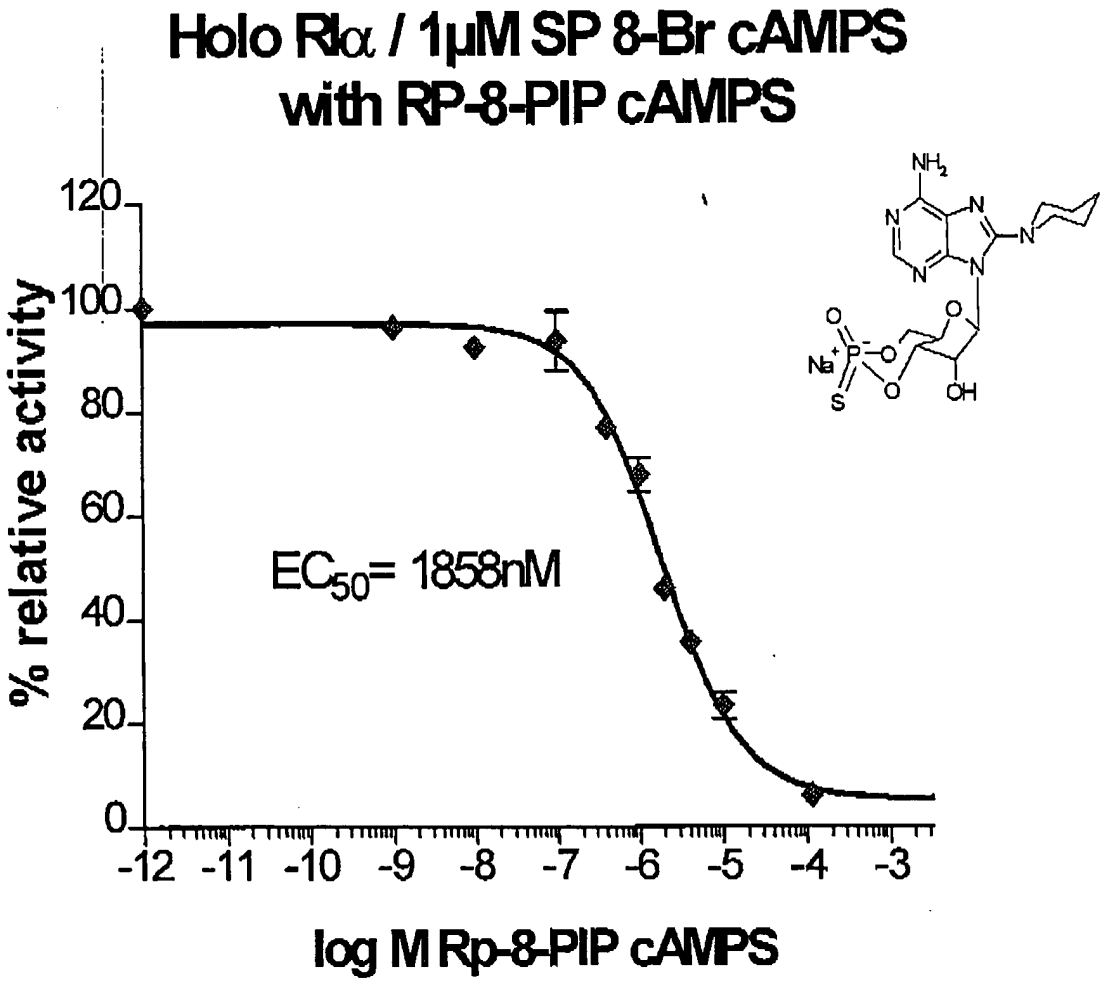


Figure 5

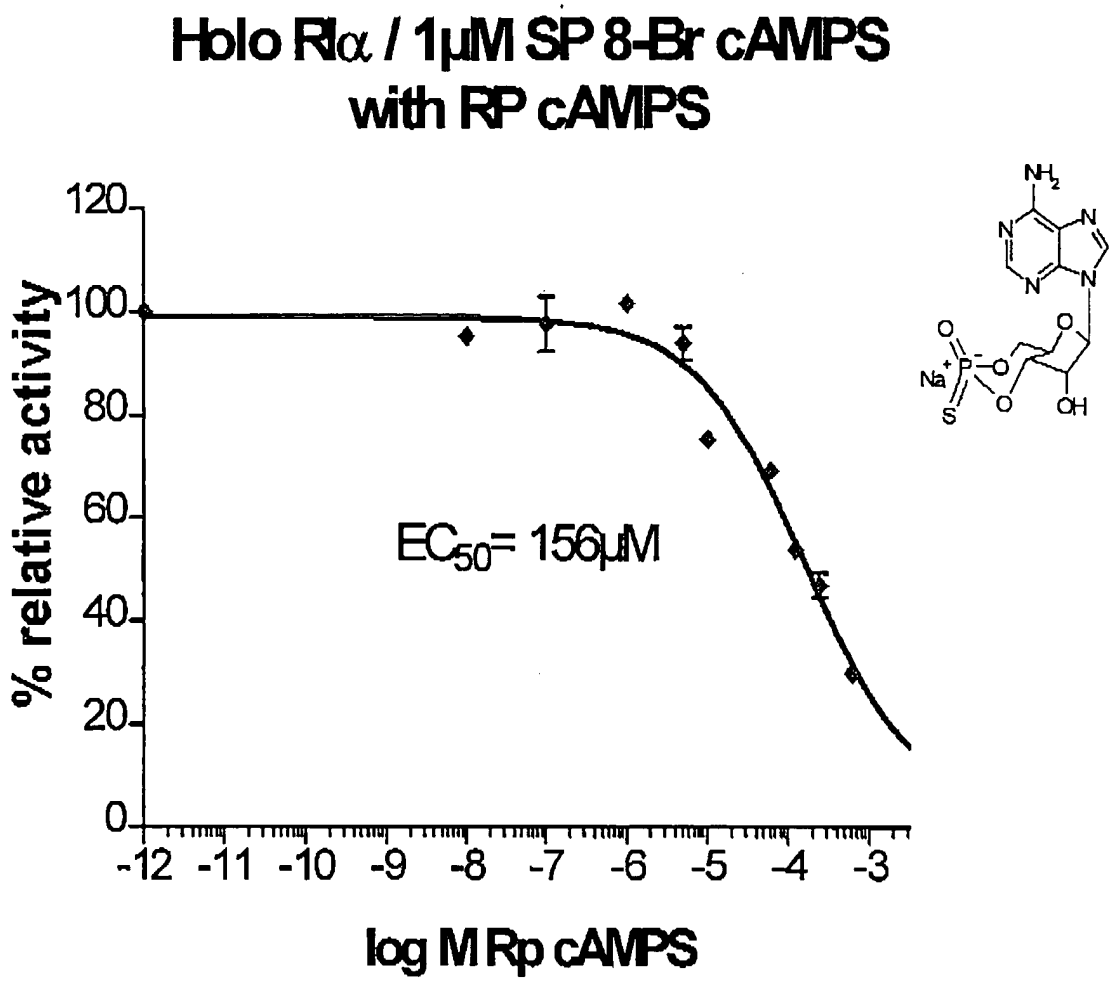


Figure 6